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PAPER

Multi-component anion relay cascade of 1-acetylcyclopropanecarboxamides, aldehydes and acrylonitrile: access to biscyanoethylated furo[3,2-*c*]-pyridinones†

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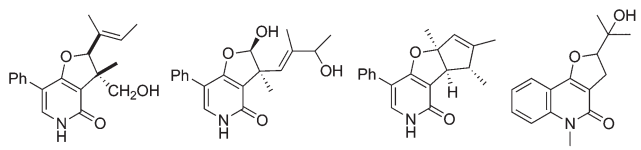
A highly efficient multi-component anion relay cascade reaction based on 1-acetylcyclopropanecarboxamides, aldehydes and acrylonitrile has been developed, which provides strategically novel and atom-economic access to biologically important biscyanoethylated furo[3,2-*c*]-pyridinones. In this one-pot transformation, up to five bonds (one C–N, one C–O and three C–C bonds) were constructed.

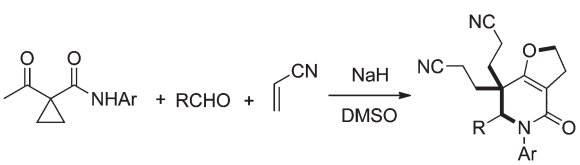
Introduction

Furo[3,2-*c*]pyridinone alkaloids are widespread among the Rutaceae family of plants[1] and display important biological activities such as antifungal,[2] antibiotic[2] and antipsychotic properties,[3] HIV protease inhibitors[4] and K-Receptor Agonists[5] (Scheme 1). Synthetic approaches for the construction of this kind of heterocycle have been reported,[6] including oxidative,[6a] or photo-induced cycloaddition[6b,c] of 4-hydroxypyridin-2(1*H*)-ones with olefins, condensation of pyridone with ethyl pyruvate and *p*-chlorothiophenol, reduction, and cyclization,[6d] rhodium-mediated dipolar cycloaddition,[6e] palladium(0)-catalyzed Suzuki[6f] or Sonogashira[6g] coupling, and other methods such as multi-component reactions.[6h] Since most methods may suffer from tedious steps, low yields and poor regioselectivity, the development of new and efficient synthetic methods toward highly functionalized furo[3,2-*c*]pyridinones is still required.



Scheme 1 Naturally occurring alkaloids containing furo[3,2-*c*]pyridinone Motif.

Recently, Dong *et al.* reported an efficient route to 2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-ones *via* a Vilsmeier-type reaction from 1-aminoalkenoyl-1-carbamoylcyclopropanes in the presence of Tf_2O in DMF.[7] In our research on the synthetic potential of β-ketoamides bearing both electrophilic and nucleophilic centers toward various carbo- and heterocycles,[8] we developed facile and straightforward protocols to construct furo[3,2-*c*]pyridinones from 1-alkenoylcyclopropanecarboxamides *via* either an aza-oxy-carbanion relay cascade[8a] or halonium-initiated electrophilic cascades.[8b] Anion relay chemistry (ARC) has been demonstrated as an effective tactic for diversity-oriented synthesis of architecturally complex natural and unnatural products.[9] In our continued work, we aimed to further exploit the preparation of diversely functionalized furo[3,2-*c*]pyridinones through a multi-component anion relay cascade reaction (Scheme 2). Multi-component reactions have been refined in recent years as powerful and useful tools in synthetic chemistry and have attracted increasing attention due to the advantages of greater efficiency, atom economy, and structural diversity and complexity.[10] The development of multi-component reactions based on appropriately substituted cyclopropanes has been reported by us[8e] and several other research groups.[11] In the



Scheme 2 Multi-component cascade reaction leading to highly substituted furo[3,2-*c*]pyridinones.

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†Electronic supplementary information (ESI) available: Experimental details and characterization for all new compounds and crystal structure data (CIF file). CCDC reference numbers 796156 (**3a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25550b

present reaction, a mixture of 1-acetylcyclopropanecarboxamides, aldehydes and acrylonitrile was subjected to the one-pot reaction, in which acrylonitrile was selected as the external electrophile (*i.e.*, anion acceptor). Acrylonitrile, as a useful synthon, has found wide application in organic synthesis.[12] As a result of the research, a multi-component anion relay cascade was established and highly functionalized biscyanoethylated furo[3,2-*c*]-pyridinones were efficiently synthesized.

Results and discussion

Initially, the model reaction of 1-acetyl-*N*-phenylcyclopropanecarboxamide **1a** (1.0 mmol), 4-methylbenzaldehyde **2a** (1.1 mmol) and acrylonitrile (1.2 mmol) in DMSO (4.0 mL) was examined under basic conditions (Table 1).[13] To our surprise, biscyanoethylated furo[3,2-*c*]pyridinone **3a** (instead of the monocyanoethylated counterpart), was obtained in 39% yield (Table 1, entry 1). The structure of **3a** was confirmed by the X-ray single-crystal diffraction (Fig. 1).[14] Encouraged by this preliminary result, we increased the amount of acrylonitrile to 2.5 equiv under the same conditions. Gratifyingly, the yield of **3a** was significantly improved to 88% (Table 1, entry 2). A further increase in the amount of acrylonitrile to 5.0 equiv was not required (Table 1, entry 3). Either cutting down the amount of NaH to 1.2 equiv (Table 1, entry 4)[15] or lowering the temperature to 60 °C (Table 1, entry 5) led to decreased yield. Reactions performed in THF or DMF gave complicated mixtures (Table 1, entries 6 and 7). Except NaH, other bases like *t*-BuONa and *t*-BuOK, were also tested, but resulted in low yields (Table 1, entries 8 and 9).

Under the optimized conditions, a range of multi-component reactions were carried out with various doubly-EWG activated substrates **1** and aldehydes **2** (Table 2). The reactions proceeded smoothly to afford the corresponding highly substituted furo[3,2-*c*]pyridinones **3** in good to excellent yields. The aryl substituents Ar on the N atom of substrates **1** may be either electron-rich or electron-deficient (Table 2, entries 1–4).[16] The scope of aldehydes **2** was also broad, including benzaldehyde (Table 2, entry 5), electron-rich aryl aldehydes (Table 2, entries 6 and 7), electron-deficient aryl aldehydes (Table 2, entries 8 and 9), heteroaryl aldehydes (Table 2, entries 11 and 12), and an alkenyl aldehyde (Table 2, entry 14). However, multi-component reactions with (hetero)arylaldehydes like 2-nitrobenzaldehyde and pyridine-4-carboxyaldehyde containing strong electron-withdrawing groups did not give satisfactory results (Table 2, entries 10 and 13).[17] The reaction with alkylaldehydes like pivalaldehyde also gave a complex mixture (Table 2, entry 15). All products were characterized on the basis of the spectral and analytical data (see the ESI†).[18]

In an isolated experiment, the reaction of **1a** (1.0 mmol), **2a** (1.1 equiv) and acrylonitrile (2.5 equiv) with NaH (2.5 equiv) as the base in DMSO (4.0 mL) at 80 °C was quenched with water after proceeding for 1 h. As a result, 3-(4,8-dioxo-5-phenyl-6-(*p*-tolyl)-5-azaspiro[2.5]octan-7-yl)propanenitrile **4** was isolated in 67% yield, along with the formation of furo[3,2-*c*]pyridinone **3a**

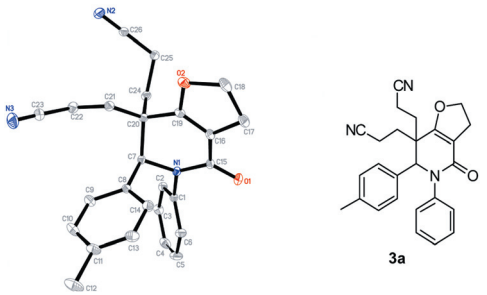
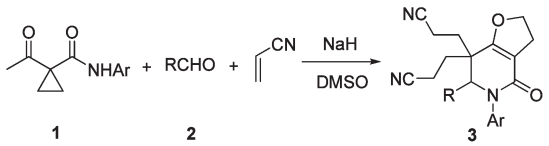


Fig. 1 ORTEP drawing of **3a**.

Table 2 Synthesis of biscyanoethylated furo[3,2-*c*]pyridinones[a]

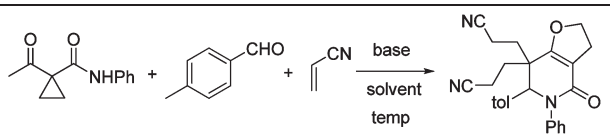


1 2 3

Entry	Ar	R	3	Yield[b] (%)
1	Ph	4-MeC_6H_4	**3a**	88
2	4-ClC_6H_4	4-MeC_6H_4	**3b**	82
3	4-OMeC_6H_4	4-MeC_6H_4	**3c**	88
4	2-Cl-4-OMeC_6H_3	4-MeC_6H_4	**3d**	86
5	Ph	Ph	**3e**	76
6	Ph	2-MeC_6H_4	**3f**	85
7	Ph	3,4-$O_2CH_2C_6H_3$	**3g**	92
8	Ph	4-ClC_6H_4	**3h**	78
9	Ph	2-ClC_6H_4	**3i**	81
10	Ph	2-$NO_2C_6H_4$	**3j**	—[c]
11	Ph	2-Furyl	**3k**	85
12	Ph	2-Thienyl	**3l**	93
13	Ph	4-Py	**3m**	—[c]
14	Ph	PhCH=CH	**3n**	90
15	Ph	*t*-Bu	**3o**	—[c]

[a] Reactions were carried out with **1** (1.0 mmol), **2** (1.1 equiv), acrylonitrile (2.5 equiv) in the presence of NaH (2.5 equiv) in DMSO (4.0 mL) at 80 °C for 5 h. [b] Isolated yield. [c] Complex mixture was observed.

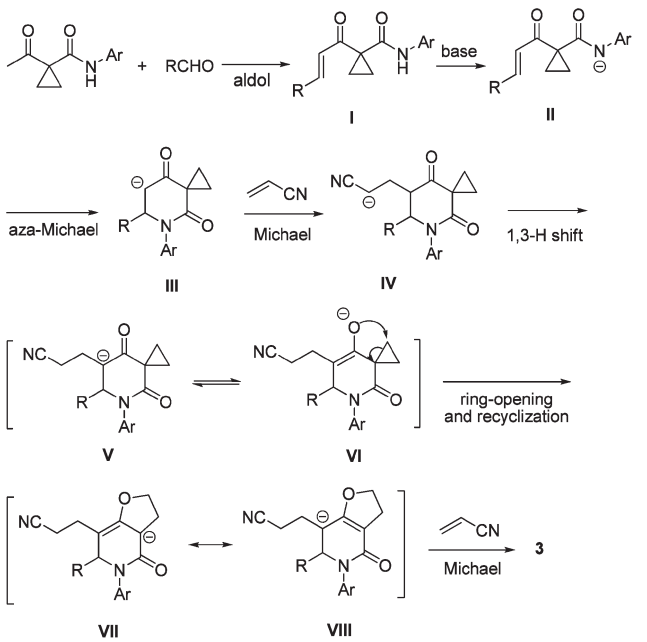
Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

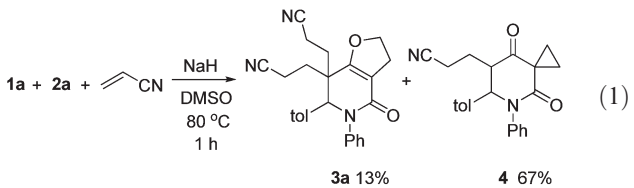
Entry	Base (equiv)	Acrylonitrile (equiv)	Solvent (mL)	*T* (°C)	Yield[b] (%)
1	NaH (2.5)	1.2	DMSO	80	39
2	NaH (2.5)	2.5	DMSO	80	88
3	NaH (2.5)	5.0	DMSO	80	87
4	NaH (1.2)	2.5	DMSO	80	55
5	NaH (2.5)	2.5	DMSO	60	23
6	NaH (2.5)	2.5	THF	80	—
7	NaH (2.5)	2.5	DMF	80	—
8	*t*-BuONa (2.2)	2.5	DMSO	80	15
9	*t*-BuOK (2.2)	2.5	DMSO	80	45

[a] Reactions were carried out on a 1.0 mmol scale in 4.0 mL of solvent with **1a** (1.0 equiv) and **2a** (1.1 equiv). [b] Isolated yield.



Scheme 3 Possible mechanism for the multi-component anion relay cascade reaction.

in 13% yield. (eqn (1)). The result helps one to answer the question of the biscyanoethylation sequence involved in the reaction.



(1)

Based on all the results described above and our previous research,[8a] a possible mechanism for the formation of **3** is proposed, as depicted in Scheme 3. The overall transformation may involve the following steps: aldol addition/aza-Michael addition/Michael addition/1,3-H shift[19]/ring opening of cyclopropane and recyclization[20]/Michael addition. The anion relay process can be briefly described as amide anion → carbanion → enolate anion → carbanion. Final electrophile trapping terminates the relay.

Conclusion

In conclusion, we have developed an efficient multi-component anion relay cascade to construct biscyanoethylated furo[3,2-*c*]-pyridinones. The one-pot process involves aldol condensation, multiple Michael additions, 1,3-H shift, ring opening of cyclopropane and recyclization, in which up to five bonds (one C–N, one C–O and three C–C bonds[21,22]) were constructed in an atom-economic manner. Further research on multi-component cascade reactions about doubly-EWG activated cyclopropanes is currently under investigation in our laboratory.

Experimental

General methods

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C and TMS as internal standard.

Typical experimental procedure for the synthesis of furo[3,2-*c*]pyridine

General procedure for the preparation of **3** (**3a** as an example): To the stirred mixture of **1a** (203 mg, 1.0 mmol) in DMSO (4 mL) was added **2a** (0.12 mL, 1.1 mmol), acrylonitrile (0.16 mL, 2.5 mmol), and NaH (70%) (86 mg, 2.5 mmol) in one portion at 80 °C. The starting material **1a** was consumed as indicated by TLC after 5 h, the reaction mixture was cooled to room temperature and poured into water and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with water (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, petroleum ether: diethyl ether = 2 : 1) to give **3a** (362 mg, 88%).

Characterization data for furo[3,2-*c*]pyridine

3,3′-(4-Oxo-5-phenyl-6-(*p*-tolyl)-2,3,4,5,6,7-hexahydrofuro-[3,2-*c*]pyridine-7,7-diyl)dipropanenitrile (3a). White solid. m.p. 106–108 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.53–1.58 (m, 1H), 1.81–1.84 (m, 1H), 1.87–1.90 (m, 1H), 2.35 (s, 3H), 2.51–2.58 (m, 3H), 3.07–3.14 (m, 2H), 4.43 (s, 1H), 4.66 (m, 2H), 6.94–6.96 (d, J = 7.5 Hz, 2H), 7.08–7.10 (d, J = 7.5 Hz, 2H), 7.13–7.19 (m, 3H), 7.24–7.26 (m, 2H); ^{13}C NMR (CDCl3, 125 MHz): δ = 12.0, 12.9, 21.0, 27.1, 27.2, 33.3, 43.0, 72.7, 73.3, 107.0, 118.8, 119.0, 126.8, 127.0, 127.9, 128.9, 129.9, 133.4, 139.1, 141.3, 163.2, 166.5; MS calcd m/z 411.2, found 412.2 $[(M + 1)]^+$. Anal. calcd for $C_{26}H_{25}N_3O_2$: C, 75.89; H, 6.12; N, 10.21; Found: C, 76.04; H, 6.14; N, 10.28.

3,3′-(5-(4-Chlorophenyl)-4-oxo-6-(*p*-tolyl)-2,3,4,5,6,7-hexahydrofuro[3,2-*c*]pyridine-7,7-diyl)dipropanenitrile (3b). White solid. m.p. 188–190 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.55–1.59 (m, 1H), 1.81–1.84 (m, 1H), 1.88–1.93 (m, 1H), 2.06–2.15 (m, 2H), 2.35 (s, 3H), 2.48–2.58 (m, 3H), 3.07–3.13 (m, 2H), 4.41 (s, 1H), 4.67–4.74 (m, 2H), 6.88–6.90 (d, J = 9.0 Hz, 2H), 7.06–7.08 (d, J = 7.5 Hz, 2H), 7.14–7.15 (d, J = 7.0 Hz, 2H), 7.20–7.22 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.2, 13.1, 21.1, 27.3, 27.4, 33.5, 43.1, 73.0, 73.5, 107.2, 118.5, 118.8, 128.0, 128.4, 129.2, 130.1, 132.5, 133.1, 139.6, 139.8, 163.3, 166.8. MS calcd m/z 445.2, found 446.2 $[(M + 1)]^+$. Anal. calcd for $C_{26}H_{24}Cl\,N_3O_2$: C, 70.03; H, 5.42; N, 9.42; Found: C, 70.21; H, 5.47; N, 9.51.

3,3′-(5-(4-Methoxyphenyl)-4-oxo-6-(*p*-tolyl)-2,3,4,5,6,7-hexahydrofuro[3,2-*c*]pyridine-7,7-diyl)dipropanenitrile (3c). White solid. m.p. 185–187 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.56–1.63 (m, 1H), 1.79–1.83 (m, 1H), 1.86–1.89 (m, 1H), 2.05–2.13 (m, 2H), 2.35 (s, 3H), 3.06–3.13 (m, 2H), 3.74 (s,

3H), 4.56 (s, 1H), 4.65–4.72 (m, 2H), 6.75–6.77 (m, 2H), 6.82–6.84 (m, 2H), 7.09 (s, 2H), 7.12–7.14 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.2, 13.1, 21.1, 27.3, 27.3, 33.6, 43.0, 55.3, 73.3, 73.4, 107.3, 114.3, 118.6, 118.9, 128.1, 128.4, 128.0, 133.5, 134.0, 139.3, 158.2, 163.5, 166.3. MS calcd m/z 441.2, found 442.2 $[(M + 1)]^+$. Anal. calcd for $C_{27}H_{27}N_3O_3$: C, 73.45; H, 6.16; N, 9.52; Found: C, 73.61; H, 6.19; N, 9.65.

3,3′-(5-(2-Chloro-4-methoxyphenyl)-4-oxo-6-(*p*-tolyl)-2,3,4,5,6,7-hexahydrofuro[3,2-*c*]pyridine-7,7-diyl)dipropanenitrile (3d). White solid. m.p. 182–184 °C. ^{1}H NMR (500 MHz, CDCl3): δ = 1.72–1.77 (t, J = 24.5 Hz, 2H), 1.87 (s, 1H), 2.05 (s, 1H), 2.12 (s, 1H), 2.34 (s, 3H), 2.57–2.61 (t, J = 20.5 Hz, 3H), 3.07–3.10 (t, J = 16.0 Hz, 2H), 3.82–3.86 (d, J = 20.0 Hz, 3H), 4.38 (s, 1H), 4.67–4.71 (m, 2H), 6.63 (s, 1H), 6.82–6.84 (d, J = 6.5 Hz, 1H), 7.12–7.15 (t, J = 16.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.2, 12.8, 27.2, 27.6, 32.8, 42.9, 55.8, 70.5, 73.3, 106.6, 112.6, 118.9, 119.0, 124.8, 128.5, 129.3, 129.8. 130.8, 132.8, 139.2, 153.6, 163.3, 167.1. MS calcd m/z 475.2, found 476.2 $[(M + 1)]^+$. Anal. calcd for $C_{27}H_{26}ClN_3O_3$: C, 68.13; H, 5.51; N, 8.83; Found: C, 68.01; H, 5.46; N, 8.94.

3,3′-(4-Oxo-5,6-diphenyl-2,3,4,5,6,7-hexahydrofuro[3,2-*c*]pyridine-7,7-diyl)dipropanenitrile (3e). White solid. m.p. 86–88 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51–1.56 (m, 1H), 1.80–1.83 (m, 1H), 1.83–1.91 (m, 1H), 2.06–2.15 (m, 2H), 2.52–2.59 (m, 3H), 3.08–3.14 (m, 2H), 4.48 (s, 1H), 4.66–4.73 (m, 2H), 6.94–6.95 (d, J = 7.5 Hz, 2H), 7.16–7.22 (m, 1H), 7.23–7.27 (m, 2H), 7.33–7.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.1, 13.0, 27.3, 33.5, 43.0, 73.1, 73.4, 107.2, 118.7, 118.8, 126.9, 127.0, 128.1, 129.0, 129.3, 136.6, 141.2, 163.2, 166.4. MS calcd m/z 397.2, found 398.2 $[(M + 1)]^+$. Anal. calcd for $C_{25}H_{23}N_3O_2$: C, 75.54; H, 5.83; N, 10.57; Found: C, 75.36; H, 5.75; N, 10.65.

3,3′-(4-Oxo-5-phenyl-6-(*o*-tolyl)-2,3,4,5,6,7-hexahydrofuro[3,2-*c*]pyridine-7,7-diyl)dipropanenitrile (3f). White solid. m.p. 206–208 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.53–1.59 (m, 1H), 1.80–1.85 (m, 2H), 1.98 (s, 3H), 2.00–2.05 (m, 1H), 2.18–2.22 (m, 1H), 2.56–2.62 (m, 3H), 3.09–3.16 (m, 2H), 4.70–4.85 (m, 2H), 4.85 (s, 1H), 6.89–6.90 (d, J = 7.5 Hz, 2H), 7.09–7.11 (t, J = 8.0 Hz, 1H), 7.19–7.20 (d, J = 7.5 Hz, 2H), 7.22–7.27 (m, 3H), 7.57–7.59 (t, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.4, 13.1, 19.9, 27.3, 27.7, 34.9, 43.0, 67.6, 73.4, 107.3, 118.6, 118.9, 127.1, 127.2, 127.4, 129.1, 131.6, 135.4, 135.5, 141.0, 163.0, 166.2. MS calcd m/z 411.2, found 412.2 $[(M + 1)]^+$. Anal. calcd for $C_{26}H_{25}N_3O_2$: C, 75.89; H, 6.12; N, 10.21; Found: C, 76.02; H, 6.14; N, 10.25.

3,3′-(6-(Benzo[*d*][1,3]dioxol-5-yl)-4-oxo-5-phenyl-2,3,4,5,6,7-hexahydrofuro[3,2-*c*]pyridine-7,7-diyl)dipropanenitrile (3g). White solid. m.p. 120–122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.72–1.84 (m, 2H), 1.89–1.94 (m, 1H), 2.08–2.16 (m, 2H), 2.47–2.56 (m, 3H), 3.03–3.09 (m, 2H), 4.38 (s, 1H), 4.66–4.72 (m, 2H), 6.00–6.01 (d, J = 4.0 Hz, 2H), 6.56 (s, 1H), 6.71–6.72 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 6.95–6.97 (d, J = 7.5 Hz, 2H), 7.19–7.22 (t, J = 14.5 Hz, 1H), 7.26–7.29 (t, J = 15.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.2, 13.0, 27.1, 33.4, 43.0, 72.9, 73.4, 101.6, 107.0, 107.7, 108.6, 118.6, 118.9, 122.1, 127.0, 127.1, 129.0, 130.2, 141.2, 148.2, 148.4, 163.0, 166.6. MS calcd m/z 441.2, found 442.2 $[(M + 1)]^+$. Anal. calcd for $C_{26}H_{23}N_3O_4$: C, 70.73; H,5.25; N, 9.52; Found: C, 70.56; H, 5.23; N, 9.45.

3,3′-(6-(4-Chlorophenyl)-4-oxo-5-phenyl-2,3,4,5,6,7-hexahydrofuro[3,2-*c*]pyridine-7,7-diyl)dipropanenitrile (3h). White solid. m.p. 204–206 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.75–1.79 (m, 2H), 1.90–1.94 (t, J = 19.5 Hz, 1H), 2.13–2.19 (m, 2H), 2.50–2.59 (m, 3H), 3.06–3.13 (m, 2H), 4.49 (s, 1H), 4.67–4.74 (m, 2H), 6.91–6.93 (d, J = 8.0 Hz, 2H), 7.15–7.21 (m, 3H), 7.25–7.26 (d, J = 6.5 Hz, 2H), 7.28–7.33 (t, J = 25.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.6, 13.3, 27.4, 27.5, 33.3, 43.2, 72.6, 73.8, 107.5, 118.8, 118.9, 127.3, 127.4, 129.5, 129.8, 125.3, 125.6, 141.2, 163.3, 166.8. MS calcd m/z 431.1, found 432.1 $[(M + 1)]^+$. Anal. calcd for $C_{25}H_{22}ClN_3O_2$: C, 69.52; H, 5.13; N, 9.73; Found: C, 69.75; H, 5.18; N, 9.84.

3,3′-(6-(2-Chlorophenyl)-4-oxo-5-phenyl-2,3,4,5,6,7-hexahydrofuro[3,2-*c*]pyridine-7,7-diyl)dipropanenitrile (3i). White solid. m.p. 194–196 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73–1.80 (m, 1H), 1.84–1.90 (m, 1H), 1.97–2.04 (m, 1H), 2.13–2.19 (m, 1H), 2.23–2.29 (m, 1H), 2.45–2.51 (m, 1H), 2.59–2.61 (m, 2H), 3.07–3.16 (m, 2H), 4.67–4.76 (m, 2H), 5.24 (s, 1H), 6.92–6.93 (d, J = 7.0 Hz, 2H), 7.18–7.21 (t, 1H), 7.25–7.28 (t, J = 15.0 Hz, 2H), 7.30–7.33 (m, 2H), 7.34–7.38 (m, 1H), 7.62–7.64 (t, J = 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.6, 12.9, 27.0, 27.2, 33.8, 43.2, 66.8, 73.5, 107.2, 118.5, 118.8, 126.6, 127.0, 128.0, 129.1, 129.1, 130.5, 130.5, 133.5, 134.8, 140.7, 163.1, 166.3. MS calcd m/z 431.1, found 432.1 $[(M + 1)]^+$. Anal. calcd for $C_{25}H_{22}ClN_3O_2$: C, 69.52; H, 5.13; N, 9.73; Found: C, 69.71; H, 5.15; N, 9.79.

3,3′-(6-(Furan-2-yl)-4-oxo-5-phenyl-2,3,4,5,6,7-hexahydrofuro-[3,2-*c*]pyridine-7,7-diyl)dipropanenitrile (3k). White solid. m.p. 186–188 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73–1.79 (m, 1H), 1.97–2.00 (m, 1H), 2.05–2.13 (m, 2H), 2.37–2.49 (m, 2H), 2.53–2.59 (m, 2H), 3.01–3.13 (m, 2H), 4.64 (s, 1H), 4.66–4.74 (m, 2H), 6.24–6.27 (t, J = 12.5 Hz, 1H), 6.36–6.36 (d, J = 1.5 Hz, 1H), 7.00–7.01 (d, J = 7.5 Hz, 2H), 7.20–7.26 (m, 1H), 7.29–7.32 (m, 2H), 7.40–7.40 (d, J = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 11.9, 13.1, 27.0, 27.3, 31.5, 43.4, 65.8, 73.6, 107.2, 110.6, 111.0, 118.6, 118.8, 126.6, 127.0, 129.1, 140.9, 142.9, 149.5, 163.6, 166.5. MS calcd m/z 387.1, found 388.1 $[(M + 1)]^+$. Anal. calcd for $C_{22}H_{21}N_3O_3$: C, 71.30; H, 5.46; N, 10.85; Found: C, 71.43; H, 5.52; N, 10.73.

3,3′-(4-Oxo-5-phenyl-6-(thiophen-2-yl)-2,3,4,5,6,7-hexahydrofuro[3,2-*c*]pyridine-7,7-diyl)dipropanenitrile (3l). White solid. m.p. 162–164 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.71–1.77 (m, 1H), 2.04–2.18 (m, 3H), 2.21–2.26 (m, 1H), 2.49–2.55 (m, 2H), 2.63–2.70 (m, 1H), 3.04–3.12 (m, 2H), 4.70–4.74 (d, J = 19.5 Hz, 2H), 4.72 (s, 1H), 6.75–6.76 (d, J = 7.0 Hz, 1H), 6.89–6.91 (m, 1H), 6.95–6.97 (t, J = 7.5 Hz, 2H), 7.23–7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 11.6, 13.1, 25.6, 27.1, 30.6, 43.3, 69.2, 73.8, 107.1, 118.6, 118.8, 126.3, 126.9, 127.1, 127.2, 128.7, 129.2, 138.5, 141.0, 162.8, 167.4. MS calcd m/z 403.1, found 404.1 $[(M + 1)]^+$. Anal. calcd for $C_{23}H_{21}N_3O_2S$: C, 68.46; H,5.25; N, 10.41; Found: C, 68.54; H, 5.27; N, 10.49.

(*E*)-3,3′-(4-Oxo-5-phenyl-6-styryl-2,3,4,5,6,7-hexahydrofuro-[3,2-*c*]pyridine-7,7-diyl)dipropanenitrile (3n). White solid. m.p. 201–203 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.91–1.93

(d, J = 9.0 Hz, 1H), 2.12–2.15 (t, J = 14.0 Hz, 1H), 2.23–2.25 (t, 1H), 2.41–2.47 (m, 3H), 2.51–2.55 (m, 2H), 3.00–3.06 (m, 2H), 4.11 (d, J = 6.0 Hz, 1H), 4.67–4.72 (m, 2H), 6.14–6.19 (m, 1H), 6.35–6.38 (d, J = 16.0 Hz, 1H), 7.16–7.18 (d, J = 7.5 Hz, 2H), 7.28–7.36 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 11.8, 12.9, 26.1, 27.3, 29.7, 42.4, 70.6, 73.5, 106.7, 118.7, 122.2, 126.6, 127.1, 127.8, 128.7, 129.2, 135.1, 135.9, 140.8, 163.3, 167.7, 171.7. MS calcd m/z 423.2, found 424.2 $[(M + 1)]^+$. Anal. calcd for $C_{27}H_{25}N_3O_2$: C, 76.57; H, 5.95; N, 9.92; Found: C, 76.69; H, 6.01; N, 9.99.

3-(4,8-Dioxo-5-phenyl-6-(*p*-tolyl)-5-azaspiro[2.5]octan-7-yl)-propanenitrile (4). White solid. m.p. 202–204 °C. ^{1}H NMR (400 MHz, CDCl3): δ = 1.65 (s, 1H), 1.92 (s, 1H), 2.03–2.09 (m, 2H), 2.17–2.25 (m, 2H), 2.36 (s, 3H), 2.39–2.42 (m, 2H), 2.75 (m, 1H), 4.46 (m, 1H), 6.88–6.90 (d, J = 86.0 Hz, 2H), 6.97–6.99 (d, J = 99.5 Hz, 2H), 7.16–7.18 (d, J = 98.0 Hz, 2H), 7.29–7.35 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.5, 12.6, 21.1, 23.6, 25.3, 27.6, 29.6, 33.4, 53.6, 70.2, 117.9, 118.7, 127.0, 127.2, 128.0, 128.8, 129.6, 130.5, 133.4, 139.6, 141.5, 168.0, 205.2. MS calcd m/z 358.2, found 359.2 $[(M + 1)]^+$. Anal. calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82; Found: C, 76.89; H, 6.17; N, 7.75.

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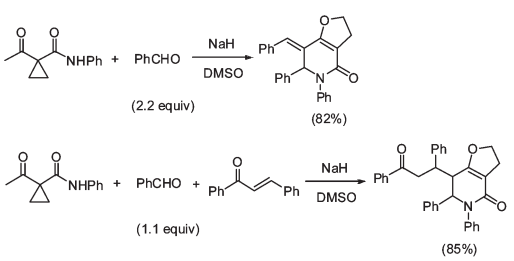

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